Attorney Docket # 4948-2PCRCE2 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Carlos PICORNELL DARDER et al.

Serial No.: 09/491,624

Filed: January 26, 2000

For: Oral Pharmaceutical Preparation Comprising an Antiulcer Activity Compound, and Process for its Production

Examiner: Sharmila S. Gollamudi
Group Art: 1615

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P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF MONA JOHANSSON UNDER RULE 132

Declaration related to US 6,132,771 to Depui et al.

The undersigned, Mona Johansson declares as follows:

1. I am an employee of LICONSA and an expert in the field of pharmaceutical technology, especially in the area of pellets formulations. I am graduated in Chemical Engineering by the Lulea University of Technology and I work at LICONSA S.A. in the development department. I have worked with pellets formulations at LICONSA and at another company since 1999.

2. I have been asked to fairly reproduce the first step of the example 5 of US patent n° 6132.771 to Depui et al. to obtain enteric coated pellets but without the separating layer before proceeding to compress them to obtain tablets (second step of Example 5).

3. Regarding the process for obtaining coated pellets (not the tablets) the Example 5 of US 6.132.771 read as follows:

Example 5

Multiple unit dosage form comprising lanzoprazole and mosapride (batch size 500 tablets).

Core material	
Lanzoprazole	400 g
Sugar sphere seeds	400 g
Hydroxypropyl methylcellulose	80 g
Sodium laurylsulfate	3 g
Water purified	1500 g
Separating layer	
Core material (acc. to above)	400 g
Hydroxypropyl cellulose	40 g
Talc	69 g
Magnesium stearate	6 g
Water purified	800 g
Enteric coating layer	
Pellets covered with a separating layer (acc. to above)	400 g
Methacrylic acid copolymer (30% suspension)	667 g
Triethyl citrate	60 g
Mono- and diglycerides (NF)	10 g
Polysorbate 80	1 g
Water purified	420 g

Suspension layering was performed in a fluid bed apparatus. Lansoprazole was sprayed onto the sugar sphere seeds from a suspension containing the dissolved binder in a water solution. Pellets covered with separating layer and enteric coating layer were produced as in example 1.

Regarding the covering process with separating layer and enteric coating layer, Example 1 reads as follows:

The prepared core material was covered with a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. In a fluid bed apparatus enteric coating layered pellets were coated with a hydroxypropyl methylcellulose solution containing magnesium stearate. The overcoating layered pellets were classified by sieving.

Since in the Example 5 a procedure for producing both the intermediate layer and the enteric coating layer is not explicitly described, I have assumed that said procedure should be also similar to those described in Example 1 without the step of forming the inert separating layer.

As observed, from an experimental point of view, Examples 1 and 5 lack many technical details, which I have completed following my best professional knowledge.

To produce both first coating and enteric coating I have used a standard bottom spray fluidized bed apparatus (model HKC-5)), and usual working conditions. The coating of the active layer was performed with an air flow of 320-340 m^3/hour, atomizing pressure 1.4 bars and a product temperature of 38° C. The coating flow was approximately 26 g/min. The process for application of the enteric coating layer was performed in similar conditions, but with a lower coating flow, approximately 20 g/min to avoid agglomeration.

As the methacrylic acid copolymer I have used Eudragit L30 D55 , which is a standard methacrylic acid copolymer for enteric coatings and it is the same copolymer used in the Example 1 of the patent application under examination.

There are many types of "mono- and diglycerides" and the Example 5 is silent on this. I have selected glyceryl monoestearate 40-55 as glidant in the enteric coating, which according to the Handbook of Pharmaceutical Excipients, Fourth Edition, page 264 (ISBN-0853694729) contains at least 40% of monoglycerides and 30-45% of diglycerides.

For a good working of the fluidized bed apparatus used, which is a 5 litres apparatus, it is necessary having higher quantities of materials than those explicitly described in the Examples. Accordingly, I have increased the amounts of the different components, but maintaining the same proportions of Example 5 and the sugar spheres had a weight of 2 kg.

The rest of details not mentioned above literally corresponds to the specifications of Examples 1 and 5.

4. The process of the first coating layer (active substance layer) was successful and performed without problem. The core materials obtained before adding the enteric coating layer had a white-creamy colour.

5. Nevertheless, important problems rose when I proceed to apply the enteric coating layer of Example 5 due to pellet's tendency to agglomerate. Even though the flow rate was decreased, agglomerate was formed. In addition, the pellets got a brownish colour already after 1 hour of coating.

Figure 1 of Annex 1 shows the evolution of the colour of the pellets obtained when reproducing example 5 of US 6.132.771 without the separating layer.

Lansoprazole pellets (core material of Example 5)

- Sample A pellets with the core material according to Example 5 of US 6.132.771, before starting to spray the enteric coating

- Sample B pellets after complete spraying of the enteric coating according to Example 5 of US 6.132.771 but without the separating layer

6. The yellowish brown colour of the obtained pellets show a degradation of the active matter and said pellets are completely unacceptable in pharmaceutical compositions.

7. The results obtained in working Example 5 of US 6.132.771 where not a surprise for me, because the prior art, for instance EP0247983 (US 4,786,505) and EP244380 (US 4,853,230) cited in the patent application, taught that an inert separating layer should be placed between the core material and the outer enteric coating layer to avoid the contact between the anti-ulcer benzimidazole compound (omeprazole, lansoprazole, pantoprazole, etc.) and the acidic component (methacrylic copolymer) of the enteric layer. Is it also mentioned that benzimidazole compounds are not stable in acidic medium, and in contact with acidic compounds they suffer degradation and develop a strong colour.

In comparison, Figure 2 of Annex 1 shows the evolution of the colour during the enteric coating process of lansoprazole pellets prepared according the Example 1 of the patent application under examination.

Lansoprazole pellets (Example 1 of the patent application under examination)

- Sample C pellets with core material prepared according to Example 1 of the patent application under examination, before starting to spray the enteric coating

- Sample D pellets after complete spraying of the enteric coating according to Example 1 of the present application under examination

The pellets obtained according to said Example 1, even not having an inert separating layer, maintained a stable white-creamy colour during the full process and, according to the data showed in Example 1, are stable during storage for several months, even at high temperature and humidity.

8. Finally, Figure 3 of Annex 1 shows the difference in colour between the final pellets obtained when reproducing example 5 of US 6.132.771 without the separating layer (Sample B) and the final pellets made according to Example 1 of the present application under examination (Sample D).

9. In my opinion the obtained results show that Example 5 of US 6,132,771 does not allow preparing the oral pharmaceutical preparations claimed in the patent application. In fact, it is my conviction that working said example 5 does not allow obtaining any acceptable lansoprazole pharmaceutical composition, due to the high colour developed as a consequence of the acidic degradation of the active compound.

10. All the statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of Application Serial No. 09/491,624 or any patent issuing thereon.

Date: 29 august 2005

Signature:

Mona Johanson
M.Sc. Chem. Eng.